REMARKS

Prior to entry of the present amendment, claims 1-29 are pending. Claims 13-17 and 20-29, due to a Restriction Requirement, are withdrawn from consideration. Claims 1-12, 18, and 19 are rejected under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 102. Applicants address each basis for rejection as follows.

Claim Amendments

Claims 1, 2, 4, 9, 10, 11, and 12 have been amended. In particular, claims 1 and 2 have been amended to require at least 90% sequence identity. Support for this amendment is found, for example, at page 16, lines 21-22, of the specification as filed. Claim 2 has also been amended to clarify that the method includes the additional step of culturing a host cell. Support for this amendment is found, for example, at page 29, line 18, to page 35, line 9, of the specification as filed.

Claim 9 as amended recites that the integration of the cassette into the endogenous chromosome "reduces the activity of the protein encoded by a nucleic acid of interest that includes the first or the second region of the endogenous chromosome." Support for this amendment is found, for example, at page 42, lines 10-29, of the specification as filed.

The dependency of claim 10 has been amended. The remaining claim amendments simply clarify the claim language. No new matter has been added by the present amendments.

Withdrawn claims 13-17 and 20-29 have been canceled. Applicants reserve the right to pursue any canceled subject matter in this or in a continuing or divisional application.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-12, 18, and 19 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, claim 1 is rejected based on the assertion that the metes

and bounds of the term "substantial sequence identity" cannot be determined from the specification or the art at the time of filing and because use of the term "cell(s)" does not clearly indicate whether the plural is claimed. Claim 1 as amended requires at least 90% sequence identity and no longer recites the word "cell(s)." These bases for the § 112, second paragraph rejection may be withdrawn.

Claim 2 is asserted to be indefinite because "it does not further limit the artificial chromosome or cassette of claim 1" and does not "clearly set forth a step of making the artificial chromosome." Applicants submit that claim 2, as amended, is free of this basis for rejection.

The Office asserts that claim 4 does not make sense because "[l]inear DNA is not 'introduced' if a circular vector is inserted." Claim 4 as amended recites that the linear DNA is *generated in* the host cell. This basis for the indefiniteness rejection may be withdrawn.

Claim 9 is rejected based on the assertion that "the integration of said cassette" lacks antecedent basis and because the claim "does not clearly set forth how the 'nucleic acid of interest' relates to the cassette, genetic modification or homologous recombination referred to in claim 1." The phrase "integration of said cassette into the genome" has been replaced with "integration of said cassette into said endogenous chromosome" which has antecedent basis in claim 1. In addition, claim 9 has been amended to recite that the nucleic acid of interest includes the first or second region of the endogenous chromosome. Applicants submit that claim 9 as amended is free of the present indefiniteness rejection.

Claim 11 is rejected as indefinite for not further limiting claim 1 because "the 'reporter' gene in claim 11 does not further limit the 'selectable marker' in claim 1." Claim 11 is also rejected because "the step of integration is unclear because it does not clearly set forth the reporter gene is operably linked to a promoter endogenous to the mammalian cell after integration." Applicants submit that the amendments to claim 11

overcome this basis for rejection.

Claim 12 is rejected as indefinite for not further limiting claim 1 because "the 'detectable protein' in claim 12 does not further limit the 'selectable marker' in claim 1." Claim 12 is also rejected because "the step of integration is unclear because it does not clearly set forth the gene encoding the detectable protein is operably linked to a gene endogenous to the mammalian cell after integration such that a fusion protein is obtained." Applicants submit that claim 12 as amended is free of this basis for rejection.

Rejection under 35 U.S.C. § 102

Claims 1-12, 18, and 19 are rejected under 35 U.S.C. § 102(a) as being anticipated by Wilson et al. (Analytical Biochemistry 296:270-278, 2001; "Wilson"). Applicants respectfully traverse this basis for rejection.

The Office states (page 4):

> Wilson transfected mouse ES cells with a yeast artificial chromosome (YAC) having a first and second region of homology with the IL-10Rα or PAARγ genes.

Applicants respectfully disagree.

Applicants submit that Wilson does not transfect mouse ES cells with a *YAC*, but rather with a *plasmid*. In support of this point, Applicants direct the Office's attention to the following passages from Wilson.

> Homologous recombination is initially performed in yeast using cassettes that function in *Saccharomyces cerevisiae*, *Escherichia coli*, and ES cells, followed by cloning or conversion of the targeted locus into a **plasmid**. The completed targeting vector can be transfected into C57BL/6 ES cells. (Abstract; emphasis added)
>
> * * *
>
> YAC clones containing the PPARγ gene were isolated ... *Apa*I was identified as a suitable cloning enzyme to target the recombinant region. **Plasmids** containing the correctly targeted region were isolated as ~22-kb *Apa*I fragments. Cassette A was replaced with Cassette E and a 10-kb *Kpn*I fragment subcloned from the 5' arm to reduce the size of the construct due

> to instability in *E. coli* and to isolate a probe that will lie outside the recombination region for assessing targeted ES cells ... The resulting targeting vector was used to obtain targeted ES cells. (bottom of right column, page 276, to top of right column, page 277; citations omitted; emphasis added)

As is evident from the above passages, Wilson excises a targeting region from a YAC and generates a plasmid that contains the targeted region for propagation in *E. coli* and transfection into ES cells.

In contrast, claim 1 requires inserting an artificial chromosome directly into one or more mammalian cells. Applicants submit that one skilled in the art would recognize that a plasmid as taught by Wilson is not an artificial chromosome. Consequently, Wilson does not describe inserting an artificial chromosome into a mammalian cell. The cited reference fails to describe each and every element required by the claims and therefore cannot anticipate claims 1-12, 18, or 19. The 35 U.S.C. § 102 rejection over Wilson should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045